Claims 1-25 are pending in this application. Claims 2-14 have been amended to provide antecedent basis, as explained in detail below. Claims 17-25 have been added. Pursuant to 37 C.F.R. § 1.173(c) support for claims 17-25 can be found in the specification including, for example, as set forth in the table below.

Claim	**Support**
17	Col. 4, lines 48-52.
18	Col. 4, lines 52-58.
19, 21	Col. 2, line 62 and Col. 3, line 4.
20, 22, 23	Col. 4, line 38 through Col. 5, line 3.
24	Col. 4, line 59 through Col. 5, line 3.
25	Col. 4, lines 44-48.

Thus, this amendment does not introduce any new matter.

Specification

The Office objected to the specification because the first paragraph did not include the cross-reference information establishing the relationship between this reissue application the issued patent. (Paper No. 5, p. 2.) Applicants have amended the first paragraph of this reissue application to include the requested cross-reference information.

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FARABOW
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1300 I Street, NW
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Drawings

The Office objected to the drawings because they contain the heading from U.S. Patent No. 5,837,531. (Paper No. 5, p. 2.) Applicants submit with this response a copy of Figures 1 and 2 without the heading from the '531 patent and respectfully request that this objection be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

1. Written Description

The Office rejected claims 1-16 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Paper No. 5, p. 3.) The Office notes that the claims read on a genus of promoters whose transcriptional activity is activated by an Epstein-Barr Virus ("EBV") antigen or a papilloma virus antigen. *Id.* Without presenting any evidence or reasons, however, the Office asserts that "the specification . . . provides sufficient description of only one species of the chimeric promoter EBNA1-RE/TP1 (column 7)." *Id.* Applicants respectfully traverse this rejection.

The PTO has the initial burden of presenting evidence or reasons why those skilled in the art would not recognize in the specification a description of the invention defined by the present claims. *In re Voss*, 194 U.S.P.Q. 267, 271 (C.C.P.A. 1977); M.P.E.P. § 2163.04. The specification clearly describes the invention as claimed. For

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Washington, DC 20005
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example, in describing how to target the expression of the heterologous sequence in the adenovirus to tumor cells, the specification explains:

> As indicated above, the heterologous DNA sequence is placed under the control of expression signals which are active specifically in tumour cells. In this way, the gene used is expressed and produces its effect only when the virus has indeed infected a tumour cell.
>
> In a preferred embodiment of the invention, they are expression signals which are induced by or active in the presence of viruses responsible for or associated with tumours. Still more preferably, an expression signal inducible by the Epstein-Barr virus (EBV) or by the papilloma virus is used within the framework of the present invention.

Col. 4, lines 27-37.

The specification further explains that EBV is associated with Burkitt's lymphoma and cancer of the nasopharnyx and that papilloma viruses are associated with cervical cancer. Col. 4, line 38 through Col. 5, line 3. In biopsies of nasopharnyx cancer, the EBV antigen, EBNA1, is regularly present. Col. 4, lines 44-45. And the human papilloma virus (HPV) antigen, E6, leads to tumor formation in HPV-infected cells by decreasing the levels of the tumor suppressor gene p53. Col. 4, lines 62-65. In addition, the specification provides a working example showing that EBNA1 and EBNA2 stimulate expression of a heterologous sequence placed under the control of an expression signal that is inducible by an EBV antigen. Thus, given applicants' disclosure, one of skill in the art would understand that any promoter sequence that is inducible by an EBV antigen or by a papilloma virus antigen could be used in applicants'

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202.408.4000
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claimed adenovirus to target heterologous gene expression to a cell that expresses an EBV or papilloma virus antigen.

The Office has provided no reasons to show why a person skilled in the art would not recognize in the specification a description of the invention defined by the present claims. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 112, first paragraph, rejection.

2. Enablement

The Office also rejected claims 1-16 under 35 U.S.C. § 112, first paragraph, asserting that the specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claimed invention. (Paper No. 5, p. 4.) The Office acknowledged that the specification enables a claim directed to:

> A replication defective recombinant adenovirus comprising a heterologous DNA sequence under the control of the chimeric promoter EBNA1-RE/TP1 which is inducible by an Epstein-Barr virus antigen or by a papilloma virus antigen.

Id. But the Office asserts that the specification is not enabling for other claimed embodiments. *Id.* Applicants respectfully traverse this rejection.

The Office has the initial burden of establishing a *prima facie* case of lack of enablement. M.P.E.P. § 2164.04. Applicants' specification disclosing how to make and use the claimed invention must be taken as complying with 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the disclosure. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1437, 1442 (Fed. Cir. 1995). The Office has questioned the scope of enablement provided by applicants' specification but has not

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1300 I Street, NW
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202.408.4000
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given any technical reasons to support the rejection. And although the Office lists the eight *Wand* factors (see M.P.E.P. § 2164.01(a)), the Office provides no analysis of these factors with respect to the presently pending claims. As stated in *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971)(emphasis in original):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Thus, the PTO has not met its initial burden of establishing a *prima facie* case of lack of enablement.

Therefore, if the Office adheres to the rejection based on a non-enabling disclosure, applicants respectfully request that the Office provide reasons why it suspects that one of skill in the art would not be able to make and/or use the claimed invention. In the absence of such reasons, applicants respectfully request that the Office reconsider and withdraw this 35 U.S.C. § 112, first paragraph, rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 2-14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Paper No. 5, p. 5.)

Specifically, the Office asserted that the recitation of "An adenovirus according to claim 1", "a replication defective recombinant adenovirus according to claim 1", and "A

FINNEGAN
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DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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composition according to claim 12" are indefinite. *Id.* The Office suggested changing these recitations from "an" and "a" to "the."

Applicants thank the Examiner for this suggestion. In an effort to expedite prosecution, applicants have amended claims 2-11 to recite "**The** adenovirus according to claim . . . ." Applicants have also amended claim 12 to recite "**the** replication defective recombinant adenovirus according to claim 1 . . . " and claim 13 to recite "**The** composition according to claim 12 . . . ." This amendment of claims 2-13 does not narrow the scope of these claims. Applicants respectfully request withdrawal of this rejection.

The Office further asserted that in claim 14, the term "viral promoter" lacks an antecedent basis from the base claim 4. *Id.* Claim 14 inadvertently depends from claim 4 rather than claim 3. Therefore, applicants have amended claim 14 to depend from claim 3. Claim 3 provides an antecedent basis for the term "viral promoter." Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102

The Office rejected claims 1, 4-6, 9-13, 15 and 16 under 35 U.S.C. § 102(b) as allegedly anticipated by WO 93/19191 ("Haddada et al."), as evidenced by Phelps et al. (J. Virol, 65, 12, 1991, pp. 6922-30) or Sample et al. (The Epstein-Barr Virus and Associated Diseases, Vol. 225, pp. 165-168, 1993) (Paper No. 5, p. 5.) Applicants respectfully traverse this rejection.

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To establish a *prima facie* case of anticipation under 35 U.S.C. § 102, the Patent Office must show that a single reference teaches each and every element of the claim. *See* M.P.E.P. § 2131. The exclusion of a claimed element, no matter how insubstantial or obvious from a reference is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 198 (Fed. Cir. 1983). Applicants respectfully assert that Haddada et al., as evidenced by Phelps et al. and Sample et al., fail to teach each and every element of the claimed invention.

Haddada et al. suggest making a recombinant adenovirus containing a heterologous DNA sequence encoding a cytokine gene under the control of the endogenous adenovirus promoter of the E1A region. Haddada et al. do not teach or suggest that the E1A-associated adenovirus promoter is inducible by an EBV antigen or a human papilloma virus antigen.

Relying on two post-filing date references, Phelps et al.[1] and Sample et al.[2], the Office asserted that the adenovirus **E2** promoter contained in the adenovirus vector of Haddada et al. "would necessarily exhibit the activity of being able to be activated by EBNA2 of EBV or by a human papilloma virus E7 antigen." *Id.* But Haddada et al. suggest placing a cytokine sequence under the control of "the precocious promoter of the **E1A region** of the adenovirus," not the E2 promoter discussed in Phelps et al. and

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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[1] Phelps et al. allegedly disclose that the adenovirus E2 early promoter is activated by a human papilloma virus E7 antigen. (Paper No. 5, p. 6)

[2] Sample et al. allegedly disclose that the EBV protein, EBNA2, can activate the adenovirus E2 promoter. (Paper No. 5, p. 6)

Sample et al.[3] Haddada et al., translation, pp. 17-18. Haddada et al. do not even mention the E2 adenovirus promoter. Furthermore, neither Phelps et al. nor Sample et al. teach that the adenovirus E1A promoter referred to in Haddada et al. is inducible by an EBV antigen or a human papilloma virus. Accordingly, Haddada et al., as evidenced by Phelps et al. or Sample et al., fail to teach every element of the claimed invention, and applicants respectfully request that this 35 U.S.C. § 102(b) rejection be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 1, and 7-8 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Haddada et al. as evidenced by Phelps et al. or Sample et al., and further in view of Woo et al. (U.S. Patent No. 5,631,236). Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the reference (or references when combined) must teach or suggest all elements of the claim. *See* M.P.E.P. § 2143.

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[3] As shown in the attached copy of Figure 11 (Exhibit 1) from Horwitz, Adenoviruses and Their Replication, *Fundamental Virology*, Chapter 28 (1986), E1A and E2 represent separate and distinct transcription units in the adenovirus genome.

Claims 7 and 8 depend indirectly from claim 1. For the reason discussed above, Haddada et al., as evidenced by either Phelps et al. or Sample et al., do not teach that the E1A-associated adenovirus promoter is inducible by an EBV antigen or a human papilloma virus antigen. Woo et al. do not remedy the deficiencies of Haddada et al. Woo et al. disclose a recombinant adenovirus vector containing the thymidine kinase gene of the herpes simplex virus. Woo et al. do not teach the E1A-associated adenovirus promoter is inducible by an EBV antigen or a human papilloma virus antigen. Accordingly, applicants respectfully request that this 35 U.S.C. § 103 rejection be withdrawn.

CONCLUSION

In view of the foregoing remarks, applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 16, 2002

By: _____
Timothy B. Donaldson
Reg. No. 43,592

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

E-mail: Timothy.Donaldson@finnegan.com
Tel.: (202) 408-4058
Fax: (202) 408-4400

STATUS OF CLAIMS PURSUANT TO 37 C.F.R. § 1.173(c)

1. (Pending) A replication defective recombinant adenovirus comprising a heterologous DNA sequence under the control of an expression signal which is inducible by an Epstein-Barr virus (EBV) antigen or by a papilloma virus antigen.

2. (Pending) The adenovirus according to claim 1, wherein the EBV antigen is EBNA 1.

3. (Pending) The adenovirus according to claim 2, wherein the expression signal consists of a chimeric promoter comprising a sequence which is activated by EBNA 1 antigen fused upstream of a viral promoter.

4. (Pending) The adenovirus according to claim 1, lacking regions of its genome which are required for replication in a target cell.

5. (Pending) The adenovirus according to claim 4, wherein said adenovirus is a type Ad5 human adenovirus or a type CAV-2 canine adenovirus.

6. (Pending) The adenovirus according to claim 1, wherein the heterologous DNA sequence comprises a gene which encodes a product toxic in a cell infected by said adenovirus.

7. (Pending) The adenovirus according to claim 6, wherein said product renders said cell sensitive to a therapeutic agent.

8. (Pending) The adenovirus according to claim 7, wherein the gene is the thymidine kinase gene and the therapeutic agent is ganciclovir or acyclovir.

9. (Pending) The adenovirus according to claim 1, wherein the heterologous DNA sequence comprises a gene which encodes a product effective to inhibit cell division.

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10. (Pending) The adenovirus according to claim 9, wherein the gene is selected from the group consisting of tumour suppressor genes, antisense sequences and ribozymes.

11. (Pending) The adenovirus according to claim 6, wherein the heterologous DNA sequence comprises a gene whose expression product induces apoptosis of a cell infected by said adenovirus.

12. (Pending) A composition comprising the replication defective recombinant adenovirus according to claim 1 and an acceptable carrier.

13. (Pending) The composition according to claim 12, in injectable form.

14. (Pending) The adenovirus of claim 3, wherein the viral promoter is the terminal protein 1 (TP1) gene promoter.

15. (Pending) An isolated cell comprising the adenovirus of claim 1.

16. (Pending) The composition of claim 12 comprising from 10^6 to 10^{10} pfu/ml of replication defective recombinant adenoviruses.

17. (Pending) The adenovirus according to claim 2, wherein the sequence which is activated by EBNA 1 antigen is the EBNA1 responsive element (EBNA1-RE).

18. (Pending) The adenovirus according to claim 14, wherein the sequence which is activated by EBNA 1 antigen is the EBNA1 responsive element (EBNA1-RE).

19. (Pending) The adenovirus according to claim 17, wherein said adenovirus is a type Ad5 human adenovirus or a type CAV-2 canine adenovirus.

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20. (Pending) The adenovirus of claim 1, wherein the expression signal comprises a promoter sequence from an Epstein-Barr virus or from a human papilloma virus.

21. (Pending) The adenovirus according to claim 20, wherein said adenovirus is a type Ad5 human adenovirus or a type CAV-2 canine adenovirus.

22. (Pending) The adenovirus according to claim 20, wherein the promoter sequence is from an Epstein-Barr virus.

23. (Pending) The adenovirus according to claim 22, wherein the promoter sequence is inducible by EBNA1.

24. (Pending) The adenovirus according to claim 1, wherein the papilloma virus antigen is E6.

25. (Pending) The adenovirus according to claim 2, wherein the expression signal comprises a BCR2 viral promoter.

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HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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